

Ionic channels as electrostatic amplifiers of charge fluctuations

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Abstract. Electrostatic interaction between ions in an ionic channel and the charge fluctuations in the channel mouth are considered. It is shown that the charge fluctuations can be enhanced in the channels with low dielectric constant and result in strong modulation of the potential barrier at the selectivity site. The effect of charge fluctuational on transition probabilities in other molecular dynamical systems is briefly discussed.

1. Introduction

Electrostatic interactions and fluctuations play crucial role in controlling transition probabilities, conduction and selectivity in nanoscale molecular systems. It is also well-known that the long-range Coulomb interaction leads to the strong correlation of ions motion and is responsible for the ions distribution and the energy fluctuations in electrolytes [9, 7]. However, in traditional approach to the calculations of the escape rates in molecular biology the charge fluctuations in the bulk are usually neglected [6]. In this paper the effect of charge fluctuations on the probabilities of transition of ions through an open ionic channel is considered.

Specifically, we consider ion transport across lipid membrane with small dielectric constant. The motion is described as a self-consistent solution of the coupled Poisson and Langevin equations for ions moving in an open ionic channel [3, 4]. The distribution of ions arrival time and the charge fluctuations at the channel mouth are investigated numerically and compared to the theoretical predictions. Next, the electrostatic energy profile of one ion in an aqueous channel through a lipid membrane charged at the selectivity site is calculated. Finally, we consider the electrostatic coupling between the charge fluctuations in the channel mouth and the energy fluctuations for the ion at the selectivity site.

It is shown that the volume charge fluctuations in the channel mouth can be modeled as a generalized short noise and result in the strong modulation of the potential barrier for an ion at the selectivity site at the sub-nanosecond time scale. It is further demonstrated that the enhanced by the channel modulation of the potential barrier is much larger as compared to the energy of Coulomb interaction between ion in the channel mouth and the ion at the selectivity site. We therefore argue that open ionic channels can be viewed as electrostatic amplifiers

of the charge fluctuations. An analytical approximation to the effect of amplification of the electrostatic interaction between the ions in the channel is provided.

2. Method

The system considered is made of three compartments of equal size. The middle block constitutes the protein through which there is a cylindrical hole representing an approximation of an open channel. The channel is bathed by a solution of NaCl on its left and right ends. The electrostatic force and potential are produced by the moving ion and fixed charge at the surface, particularly the net negative charge bared by a fraction of the protein at the channels selectivity filter. The Poisson equation is solved in 3D space with cylindrical symmetry. The electrical sources are the fixed negative charge on the protein and the ions located on the channel axis. Since the dielectric value of the aqueous pore is not yet known for narrow channels, as first approximation, we use the same dielectric value as for the aqueous bath $\epsilon_2 = 80$. The dielectric value of the protein is taken to be equal to $\epsilon_1 = 2$.

The motion of the ions is modeled within a self-consistent framework of Brownian dynamics (BD) coupled to the Poisson equation.

$$m_i \ddot{\vec{x}}_i = -m_i \gamma_i \dot{\vec{x}}_i + \left[\frac{q_i q_j}{4\pi\epsilon\epsilon_0 r_{ij}^2} + \frac{9U_0 R_c^9}{r_{ij}^{10}} \right] \frac{\vec{r}_{ij}}{r_{ij}} + F_{ch} + \sqrt{2m_i \gamma_i k_B T} \vec{\xi}_i(t), \quad (1)$$

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where m_i , x_i and q_i are the mass, position and charge of the i th ion. In the Brownian dynamics simulations, water molecules are not taken into account explicitly and are represented in Eq. (1), by an average frictional force with a friction coefficient $m_i \gamma_i$ and a stochastic force $\sqrt{2m_i \gamma_i k_B T} \vec{\xi}_i(t)$ arising from random collisions. The long range Coulomb interaction is represented by the $1/r$ potential. The addition of the pairwise repulsive $1/r^9$ soft-core interaction potential insures that ions of opposite charge, attracted by the inter-ion Coulomb force, do not collide and annihilate each other. r_{ij} is the distance between ions i and j . U_0 and R_c are respectively the overall strength of the potential and the contact distance between ions pairs [8].

We used the following parameters for the simulations:

Dielectric constants: $\epsilon_2 = 80$, $\epsilon_1 = 2$;

Masses (in kg): $m_{Na} = 3.8 \times 10^{-26}$, $m_{Cl} = 5.9 \times 10^{-26}$;

Diffusion coefficients (in $m^2 s^{-1}$): $D_{Na} = 1.33 \times 10^{-9}$, $D_{Cl} = 2.03 \times 10^{-9}$,

(Note that D is related to the friction coefficient via $D = \frac{k_B T}{m\gamma}$);

Ion radii (in Å): $r_{Na} = 0.95$, $r_{Cl} = 1.81$;

Temperature: $T = 298$ K.

Ions	$U_0 (k_B T)$	$R_c (\text{Å})$
Na-Na	0.5	3.50
Na-Cl	8.5	2.76
Cl-Cl	1.4	5.22

Table 1. Parameters used in the calculation of the short range ion-ion interaction

The dielectric force acting on the ion as it moves on the channel axis F_{ch} is calculated numerically by solving Poisson equation

$$-\nabla \cdot (\epsilon(\vec{r}) \nabla \phi(\vec{r})) = \frac{\rho(\vec{r})}{\epsilon_0}, \quad \vec{D} = \epsilon \vec{E}, \quad \vec{E} = -\vec{\nabla} \phi \quad (3)$$

using finite volume method (FVM) [5]. In Eq. (3), $\epsilon = \epsilon_k \epsilon_0$ is the space dependent dielectric function with $k = 1$ or 2 . $\epsilon_0 = 8.85 \cdot 10^{-12} CV^{-1}m^{-1}$ is the dielectric constant of empty space. ρ is the source density, ϕ is the potential, \vec{D} and \vec{E} are respectively the displacement vector and the electric field. An effective dielectric constant is introduced at the interface between water and the protein. The later procedure is more appropriate when the dielectric function present severe jump. In order to preserve the system symmetrical symmetry, the moving ion is bound to move on the channel axis. Dirichlet boundary condition is used to fix the value of the electrostatic potential at the left and right boundaries of the system as used in experimental measurement. Neumann boundary condition is used to set the value of the normal component of the electric field. Standard iterative method is used to solve algebraic linear system grown from discrete Poisson equation. The results are stored in tables allowing for the fast self-consistent BD simulations.

3. Distribution of arrival times and the charge fluctuations

In this research we are focused on estimating the effect of the charge fluctuations on the transition probabilities of the ions through an open ionic channel. To this end we would like to calculate how much time ions spend in the channel mouth and how often do they arrive to the channel mouth. Estimation of arrival time of ions at the channel mouth from a solution assuming charge neutrality and no applied field can be obtained by considering pure diffusion of ions through the hemisphere at the mouth of the channel and is given by $\tau_{ar} = 1/(2\pi z_i \aleph D_i r c_0)$; where r is the channel radius, c_0 the bulk concentration, \aleph the Avogadro number, z_i and D_i the charge valence and the diffusion coefficient of the i th ion [6, ?]. For an NaCl solution of concentration $c_0 = 500\text{mM}$, estimated arrival time $\tau_{ar} \sim 2.9 \times 10^{-9}\text{ses}$ for Na^+ and $\tau_{ar} \sim 3.8 \times 10^{-9}\text{ses}$ for Cl^- .

To estimate the charge fluctuations from the simulations we have recorded continuously (during a few microseconds) the total positive and negative charge in the channel mouth with volume $v_M = \pi r^2 * r$, where $r = 6\text{\AA}$. The arrival time was estimated by recording the interval of times between the subsequent events of ion arrival to the channel mouth. The results of simulations are summarized in the Fig. 1. It can be seen from the figure that the arrival time distribution follows exponential distribution with mean arrival time $\tau_{ar} \sim 3.6 \times 10^{-9}\text{ses}$ for Na^+ and $\tau_{ar} \sim 4.7 \times 10^{-9}\text{ses}$ for Cl^- .

This corresponds corresponding to a Poisson process as expected from the theory. The corresponding charge fluctuations at the channel mouth is represented on Fig. 1.(b).

4. Amplification of the electrostatic interaction between two ions in the channel

We now consider the effect of the charge fluctuations on the transition probabilities of the ions through an open ionic channel. First, we analyze the energy profile faced by one ion moving through the channel.

The total electrostatic energy required to move one ion from the bulk solution to a bare channel that is 30\AA long and 4\AA in radius as a function of the position of the ion is calculated as shown in the Fig. 2(a). The potential drop across the channel is $\Delta\Phi = 90\text{ mV}$, the charge at the selectivity site (at the middle of the channel) is $-1e$. Note that the value of the potential barrier for the ion at the selectivity site to exit the channel is ΔE_0 as shown in the Fig. 2 (b). We now consider the reduction of this potential barrier induced by the second ion situated at the channel mouth. The total energy of the channel as a function of the position of the first ion moving along the channel when the second ion is located at the channel mouth is shown in the Fig. 2(b) by dashed line. It can be seen that the presence of a second ion at the channel entrance decreases the energy barrier to ΔE_1 . We note the reduction of the potential barrier from ΔE_0 to ΔE_1 is much stronger in the channel with low dielectric constant. I.e. the effect of charge fluctuation is strongly enhanced by the protein low dielectric constant compared to

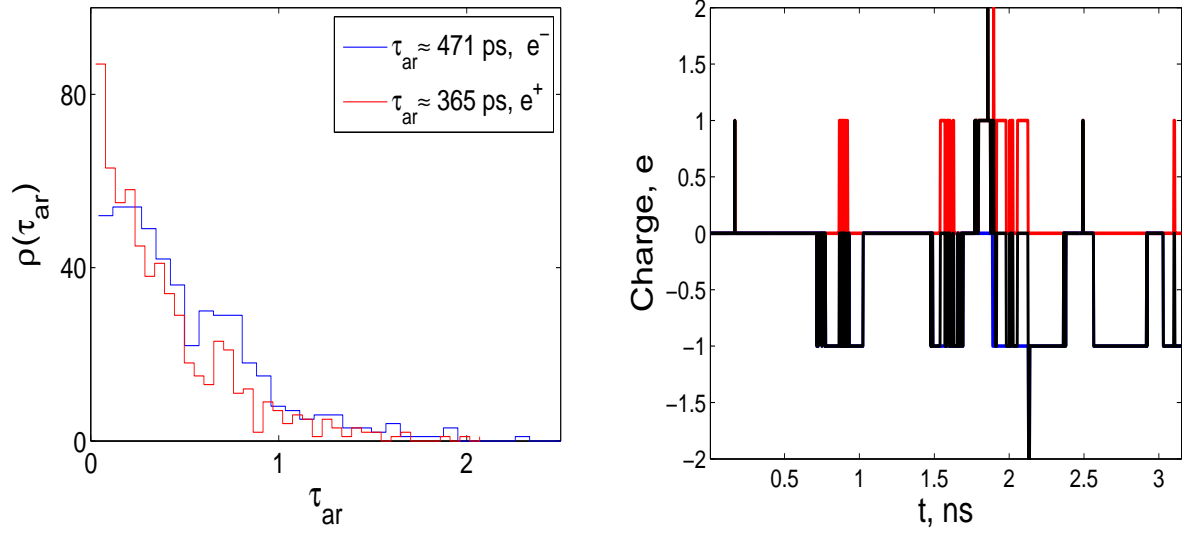


Figure 1. (a) The arrival time distributions for positive (red line) and negative (blue line) ions for cylindrical channel of radius $r = 4 \text{ \AA}$. (b) Fluctuations of the charge at the mouth entrance.

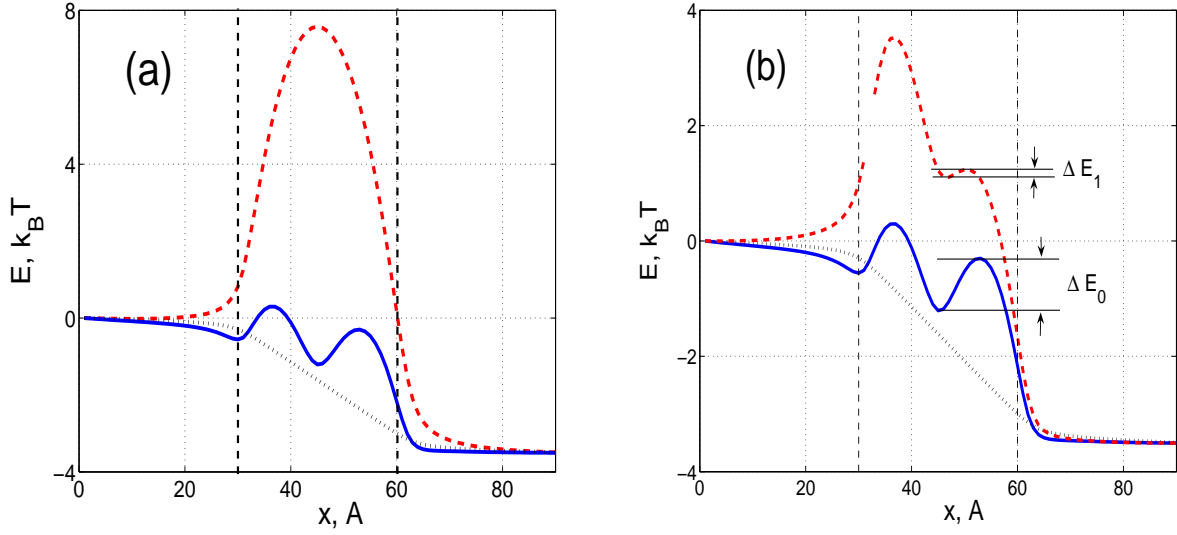


Figure 2. (a) The potential energy profiles in a cylindrical channel of radius $r = 4 \text{ \AA}$ when an electric field of 10^7 V/m is applied in the z direction. The solid (blue) and dashed (red) lines correspond to the channels with and without fixed charges, respectively. The profile of a passive channel ($\epsilon_{protein} = 80$) is indicated by the dotted (black) line. The channel is situated between 30 and 60 \AA . (b) Total energy of the channel as a function of the position of the ion when: the first ion is located at the channel mouth (dashed line); the channel is empty (solid line); no channel (dotted line). Vertical dashed-dotted lines show channel entrance. The height of the potential barrier for the ions at the selectivity site and no ion at the channel mouth is denoted ΔE_0 . In the presence of the second ion in the channel mouth this barrier is reduced to ΔE_1 .

water. in the absence of the protein walls the interaction between two ions will be purely due

to the Coulomb forces and the corresponding reduction of the potential barrier $\Delta E_C = \frac{e^2}{4\pi\epsilon_2\epsilon_0 r_{12}}$ will be much smaller than the effect induced by the channel $\Delta E_0 - \Delta E_1$.

5. Analytical approximation of the effect of the amplification

A simple one-dimensional approximation of Poisson equation for a long (length d) and narrow (radius r) channel can be derived [1, 2] and written on its dimensionless form as:

$$\begin{aligned}\ddot{\Phi} - \beta\Phi &= -\beta\Delta(1-x) - \alpha P(x) - \alpha\delta(x-x_0) - \alpha\delta(x-x_1) \\ \Phi(0) &= 0, \quad \Phi(1) = \Delta\end{aligned}\quad (4)$$

where $\beta = \frac{d^2\tilde{\epsilon}}{\epsilon_0\epsilon_{H_2O}}$ is a function of the effective dielectric parameter $\tilde{\epsilon} = \frac{\epsilon_p}{\epsilon_{H_2O}} \frac{2\epsilon_0}{r^2 \ln(d/r)}$. The factor $\alpha = \kappa^2 d^2$ where $\kappa^{-1} = \sqrt{\frac{\epsilon_0\epsilon_{H_2O}v_0 U_T}{e}}$ is the Debye length with $v_0 = \pi r^2 d$; the volume of the cylindrical channel. $U_T = k_B T$ is the thermal energy; where k_B is the Boltzmann's constant and T the absolute room temperature. $P(x)$ is the permanent charge distribution on the protein atoms; independent of the electric field. The δ function represents two moving ions at different locations x_0 and x_1 on the channel axis. Because the Poisson equation is linear the contribution from the four terms in the right hand side can be considered independently. Here we concentrate on the interaction between two ions in the channel in the absence of any external field and therefore leave only the two last terms in the eq. (4) (see, however, for the full analytical solution of the Poisson equation elsewhere).

$$\begin{aligned}\Phi(x) &= -\alpha \int_0^1 G(x,s)P(s)ds \\ &- \frac{\alpha}{\sqrt{\beta} \sinh \sqrt{\beta}} \begin{cases} \sinh \sqrt{\beta}x \sinh \sqrt{\beta}(x_0-1) + \sinh \sqrt{\beta}x \sinh \sqrt{\beta}(x_1-1), & 0 \leq x \leq x_1 \\ \sinh \sqrt{\beta}x_0 \sinh \sqrt{\beta}(x-1) + \sinh \sqrt{\beta}x \sinh \sqrt{\beta}(x_1-1), & x_1 \leq x \leq x_0 \\ \sinh \sqrt{\beta}x_0 \sinh \sqrt{\beta}(x-1) + \sinh \sqrt{\beta}x_1 \sinh \sqrt{\beta}(x-1), & x_0 \leq x \leq 1 \end{cases}\end{aligned}\quad (5)$$

Where the Green function is given by:

$$G(x,s) = \frac{1}{\sqrt{\beta} \sinh \sqrt{\beta}} \begin{cases} \sinh \sqrt{\beta}x \sinh \sqrt{\beta}(s-1), & 0 \leq x \leq s \\ \sinh \sqrt{\beta}s \sinh \sqrt{\beta}(x-1), & s \leq x \leq 1 \end{cases}\quad (6)$$

The distribution of the permanent charge is modelled using a narrow Gaussian distribution, consistent with the fact that the charge is mainly concentrated at the central part of the channel

$$P(x) = \frac{1}{\sqrt{2\pi}\sigma^2} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$$

6. Conclusion

It was shown that the energy fluctuations due to the correlation of the motion between ions in strong electrolytes can be substantially enhanced in the open ionic channels with low dielectric constant. Therefore, ion channels can be thought of as electrostatic amplifiers of the charge fluctuations. This in turn may lead to an exponentially strong modulation of the potential barrier for the ion at the selectivity site. The resulting enhancement of the transition probabilities of ions through open ionic channels can be leading order contribution to the transition probabilities calculated using standard theories that neglect the effect of charge fluctuations. The effect of electrostatic amplification of the charge fluctuations may play substantial role in the nanoscale protein dynamics, including, in particular, protein folding.

7. References

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